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Mr. Randy Segawa
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Re: Gowan Company comments on August 5, 2005 draft methidathion *Risk Characterization Document (Revision 1)*

Dear Mr. Segawa:

Gowan Company appreciates the opportunity to respond to the referenced draft risk characterization document (RCD) and also to DPR's request for comment on the potential listing of methidathion as a toxic air contaminant.

It is our understanding that DPR is soliciting comments that are relevant to the toxic air contaminant program, only, at this time. However, we believe that our earlier comments on dietary and occupational risk also continue to be relevant. Certain of the hazard and exposure assumptions previously used by DPR are reiterated in the most recent draft RCD; and they remain of great concern to us. These include several unrefined exposure inputs and also the inappropriate use of low dose linear extrapolation to calculate a completely improbable cancer potency factor. We refer DPR to our submissions of December 17, 1999 [response to August 17, 1999 *Dietary and Drinking Water Risk Assessment*], January 21, 2003 [response to October 23, 2002 *Occupational Risk Assessment Addendum*] and March 9, 2004 [response to October 3, 2003 *Risk Characterization Document Addendum: Occupational and Ambient Air Risk Assessment*].

Neither the hazard nor the exposure data support the listing of methidathion as a toxic air contaminant. Our comments are detailed, below.

1. LOW DOSE LINEAR EXTRAPOLATION IS INAPPROPRIATE

We previously have commented extensively on the inappropriate use of low-dose linear extrapolation to calculate a cancer potency factor. We reiterate our concerns that DPR's approach is completely non-reflective of the available data and is counter to the conclusions reached by other regulatory authorities.

The overwhelming weight-of-the-evidence from a robust database does not support the linear

extrapolation utilized by DPR. We find it of interest that DPR itself appears to remain largely unconvinced of the suitability of such an approach. For example, DPR states the following in the RCD [at Page 64]:

> *Although DPR toxicologists agree that the weight of evidence is limited, the mode of action is uncertain. Direct DNA interaction could not be eliminated based on the few positive genotoxicity studies.*

However, DPR also describes these studies in the following manner [at Page 64]:

> *Moreover, the genotoxicity data for methidathion were predominantly negative. The only positive results were reported in two assays of questionable biological significance (a gene conversion/forward mutation assay with Saccharomyces cerevisae and an in vitro sister chromatid exchange assay with Chinese hamster V79 cell line).*

Since the weight of evidence from an extensive and overwhelmingly negative genotoxicity database apparently is tipped on the basis of these two non-regulatory assays "of questionable biological significance" it is appropriate to examine each in some detail. We believe that DPR has overlooked several key features about these data.

In vitro SCE study

DPR appears to apportion the most evidentiary weight to an *in vitro* sister chromatid exchange (SCE) study found in the open literature. However, this study does not meet any of the main criteria necessary for an acceptable regulatory submission, and as such, it is inappropriate for inclusion in the weight of evidence. For example:

1) This is a non-GLP study. There is no indication that appropriate Quality Assurance procedures were followed in the study.

2) No method validation data are provided.

3) The relevant USEPA Guideline (OPPTS 870.5900) requires the use of positive controls. However, no positive controls were included in the assays.

4) There is insufficient detail concerning methodology to permit independent evaluation of the manner in which the assays were conducted. To mention just a few examples: the derivation of the hamster V79 cells utilized is unknown. Cell growth and maintenance conditions are critical for an acceptable regulatory study, however these parameters are unknown. The stage of cell growth at the time of treatment is not reported. OPPTS 870.5900 requires that cells are treated during the exponential growth phase; however it is unknown whether this was done. The Guidelines also require that cells are washed following exposure to the test chemical prior to replication in the presence of BrdU; however there is no indication that this critical procedural

step was included.

5) Guideline OPPTS 870.5900 requires that at least two independent cultures are used for each experimental point. It is unclear in the publication whether this procedure was followed.

6) No statistical analyses of the data were presented or are possible to reconstruct on the basis of the information provided. The "positive" results reported for methidathion were in the general range of background levels observed in controls for several of the assays with other chemicals that also are reported in the paper. Since the reported methidathion response was marginal, at best, statistical analyses are essential to corroborate a "positive" finding. Also, it must be reiterated that this study did not employ positive controls.

7) The method of scoring the SCEs must be taken on faith. No details are provided.

It also warrants mention that DMSO was used as the vehicle in this study. Such an experimental design may be useful as a lowest-tier screening assay. However, given the known properties of this industrial solvent to enhance penetration and transport in biological systems, we question the relevance of any experimental finding associated with this vehicle to profile actual hazard from exposure to methidathion.

We are concerned that DPR continues to discount the negative *in vivo* SCE study from the weight-of-the-evidence. There was no indication of any increase in SCE frequency in the *in vivo* regulatory study with Chinese hamsters at a dose of 68 mg/kg. Since this dose level exceeds the LD_{50} for methidathion in hamsters [RCD, at page 22], it is clear that the *in vivo* study utilized an extreme experimental challenge for SCE induction. The results clearly show that methidathion is negative for SCE effects at the highest dose level possible to achieve in a living animal.

In vitro *Saccharomyces* gene conversion/forward exchange assay

This "assay" apparently reports positive results in yeast at dosages of 625 to 10,000 µg/ml, using a DMSO vehicle. These test concentrations exceed the water solubility of methidathion [220 ppm, as cited in RCD at page 12] by about 2.8x to 45x.

Apart from the lack of biological relevance of the extreme dose levels examined, we take considerable exception to inclusion of these "data" into the evidentiary weight because no study is available for independent evaluation. The "data" appear to be only a citation of a citation. Since no details concerning the conduct of the work are available for review, DPR must reject the data altogether. To utilize the referenced findings as a key pillar in the methidathion weight-of-evidence carcinogenicity evaluation is not appropriate.

Conclusions on the weight-of-the-evidence

DPR cites the *in vitro* SCE and yeast assays as key evidence supporting low dose linear

extrapolation and has calculated an extreme cancer potency factor for methidathion. However, this approach is simply not reflective of the overwhelmingly negative genotoxicity database for methidathion.

The yeast assay must be rejected entirely from the weight of evidence evaluation because no study details are provided in the citation cited by DPR. We note also that the "positive" data are inconsistent with the negative *S. typhimurium* and *E. coli* reverse mutation assays. Furthermore, higher-tiered testing in the mouse dominant lethal and hamster micronucleus tests were negative and are of greater evidentiary weight.

We have noted a variety of methods problems and departures from regulatory guidelines associated with the *in vitro* SCE study. The marginal results reported in this *in vitro* study are not supported by the *in vivo* SCE data and should not be accorded preferential evidentiary weight.

We do not believe that the marginal and/or uncorroborated findings in either of the cited lower-tiered assays justify the calculation of a cancer potency factor. Our view is consistent with that of the USEPA. Should DPR continue to disagree with our conclusion we suggest again that an independent peer review of the data would be appropriate.

2. AIR MONITORING DATA AND RISK ASSESSMENTS

DPR has presented air monitoring data and Margin of Exposure and oncogenic risk assessments. The air monitoring was done in 1991 and is summarized in Royce, 1993 [cited in HS-1805 at page 42]. In this section we identify and address scientific issues with the air monitoring and the subsequent handling of the data.

Analytical Methods

The oxon degradate of methidathion is expected to be found in low concentrations relative to the parent. It was found in substantially greater concentrations. DPR concluded that the oxon data were unreliable and did not calculate molecular equivalents for addition to measured parent compound. We agree.

The Royce paper also noted that there was a positive bias in the methidathion analytical method - this would lead to overestimates of air concentrations. We examined all data that could be considered "quality control samples": extraction efficiency; retention efficiency; storage stability; ice chest stability; field controls; extraction controls; and, audit samples.

Percents of analyte recovered from fortified samples are presented on the following page:

Count:	60
Mean:	119%
SD	20%
%CV	17%
Count >120%	27
Mode	123%

Nearly 50% of the recoveries exceeded 120% and 84% of the recoveries exceeded 100%. Under USEPA Residue Chemistry Test Guidelines (OPPTS 860.1340, Residue Analytical Method), the method would be unacceptable as recoveries were outside the range of 70-to-120% and the coefficient of variation was high. We suggest eliminating some of the positive bias by adjusting the raw residue values for the most frequently observed recovery, the mode of 123%.

Ambient Air Monitoring

Table 4 of HS-1805 presents the data from the 5 sites monitored in Tulare County in 1991. The site with the highest residues was selected for the exposure and risk assessments - the roof of the Jefferson Elementary School (Site J). We note that the value of 0.32 $\mu g/m^3$ for the first day of monitoring is in error - it is 0.032 as reported in Royce. Also, the erroneous mean in Table 4 does not comport with a different erroneous mean in Table 11. This error cascades through all the assessments as the mean, 95th percentile, etc. become substantially lower with the corrected value. We also note that the regulatory convention for handling less-than-limit-of-quantitation (LOQ) values was not followed.

When a residue is less than LOQ, but greater than the limit of detection (LOD), the accepted procedure is to use one-half the LOQ value. In Table 4, nine of the 17 values were <LOQ but were represented with an "apparent" residue. Another two samples were <LOD and were properly represented as one-half the LOD. Given that only six of the 17 samples had quantifiable residues, and that the quantitation was positively biased, we recommend handling the data by convention: adjust raw residue values for the positive bias; identify <LOD and <LOQ values and substitute one-half the appropriate value:

Adjusted ambient air residues are presented on Page 6 of this submission.

Table I.—Adjusted ambient air residues

Ambient Air--Site J--ug/m^3			
Raw	HS-1805	Adjusted ug/m^3	
0.032	0.320	0.026	0.026
<LOQ	0.018	<LOQ	0.015
<LOQ	0.018	<LOQ	0.015
<LOQ	0.012	<LOQ	0.015
<LOQ	0.011	<LOQ	0.015
<LOD	0.005	<LOD	0.005
<LOD	0.005	<LOD	0.005
0.560	0.560	0.455	0.455
0.300	0.300	0.244	0.244
0.036	0.036	<LOQ	0.015
<LOQ	0.023	<LOQ	0.015
0.036	0.036	<LOQ	0.015
0.031	0.031	<LOQ	0.015
<LOQ	0.028	<LOQ	0.015
<LOQ	0.025	<LOQ	0.015
<LOQ	0.015	<LOQ	0.015
<LOQ	0.014	<LOQ	0.015
Count	17		17
Mean	0.086		0.054
SD	0.156		0.118
		95th Pctl.	0.198
		0.66=Pctl	99.5

LOD=0.01, LOQ=0.03 ug/m^3
Adjusted for 123% method bias.
Percentiles from lognormal model, @Risk, 50,000 iterations.

In HS-1805 it is noted that 95th percentile values are used for acute assessments rather than higher percentiles because those estimates are less reliable and tend to be overestimates. However, for ambient air, DPR estimated the upper 90th percent confidence limit on the lognormally calculated 95th percentile. When the original miscalculated lognormal distribution was modeled with @Risk (an Excel probabilistic modeling add-in, Latin hypercube, 50,000 iterations), the 95th percentile was 0.301 and the DPR value of 0.66 µg/m^3 was the 99th percentile - more than double the 95th percentile. There is no scientific or policy basis for using any value greater than the 95th percentile modeled from the adjusted values. There is also no scientific basis for assuming exposure at the highest month of use in the county with the greatest use to continue seasonally or for any number of months annually (here 9 months, where the maximum use in two of the 9 months is only ~30% of the monitored month). This approach grossly overestimates exposure. To assume that monitoring from the roof of the Jefferson Elementary

School represents exposure to the general public (see title of Table 28 in Lewis, 2005, as cited in HS-1805 at page 41), is also not based in science. Nevertheless, we have re-calculated exposures and margins of exposure per DPR methodology with the adjusted residue values.

Table II.—Exposures and margins of exposure from ambient air at Site J.

Ambient Air--Site J		
	ug/kg/day	MOE
Acute--Infants	0.117	2,568
Acute--Adults	0.055	5,411
Seasonal--Infants	0.032	6,297
Seasonal--Adults	0.015	13,268
Annual--Infants	0.024	6,297
Annual--Adults	0.011	13,268
Mean ug/m^3	0.054	
95th pctl. ug/m^3	0.198	
Infant inhal rate	0.59	m^3/kg/day
Adult inhal rate	0.28	m^3/kg/day
Acute NOAEL	0.3	mg/kg/day
Seasonal NOAEL	0.2	mg/kg/day
Annual NOAEL	0.15	mg/kg/day
Annual use months	9	

There should be no concerns about exposure to residues in ambient air.

Bystander Exposure

A single application in Tulare County was monitored for airborne residues during and through 20 hours after application in 1991. The study plans noted that the prevailing wind was from the NW. Two sampling stations were placed SE of the citrus grove, presumably to collect representative samples from a downwind border area 15 to 150 yards from the application. A single sampling station was placed 25 yards to the north. The wind was uncooperative and compromised the study plan by changing from the NW pre-application and blowing from the SW during the first 14 hours of the monitoring, then reversing and blowing from the NW. Only major wind directions were reported for each monitoring period - we assume that with changing winds there was variation in the direction during each monitoring period. DPR chose to use only the North Station values. However, the North Station did not cover a representative area, as intended by the two SE stations. It is unlikely that a person would remain stationary at one location 25 yards from an orchard for a full day. Given that the wind blew onto all stations, the best representation of airborne residues would come from all samples collected, as shown on the following page.

Table III.—Bystander airborne residues and MOE.

	Stations and ug measured:					
Period	N	SE1	SE2	Hours	m^3/sample	ug/m^3
0	ND	ND	ND	Pre-application		
1	0.28	0.05	0.05	7.75	0.86	0.15
2	0.19	0.05	0.05	2.00	0.22	0.44
3	0.59	0.05	0.05	3.83	0.42	0.55
4	0.62	0.95	0.21	6.83	0.76	0.78
Sum:	1.68	1.1	0.36	20.41		
					TWA, Raw=	0.463
					TWA, adjusted=	0.376
123%	Adjustment factor for positive bias.					
0.1 ug/sample=LOD and LOQ					Infant MOE	1,351
Infant inhal rate		0.59	m^3/kg/day		Adult MOE	2,846
Adult inhal rate		0.28	m^3/kg/day			
Acute NOAEL		0.3	mg/kg/day			

We also note that the time-weighted-average (TWA) $\mu g/m^3$ presented by DPR was in error - it was the overall average and was not time-weighted. Given these MOE, and the extremely conservative underlying assumptions, there should be no concern about bystander exposure.

Oncogenic Risks

DPR calculated maximum likelihood estimate (MLE) and upper bound (UB) oncogenic potency factors of 0.34 and 0.53 $(mg/kg/day)^{-1}$, an approach that is not supported by the toxicity database. DPR then did a crude oncogenic risk assessment assuming that the population of California was tethered to the roof of the Jackson Elementary School in Tulare County for nine months per year at the highest Tulare County exposure month for a lifetime. This approach is obviously not consistent with the accepted approach for exposures to residues in food and water: the general adult population per capita mean is estimated and applied to the potency factors. The accepted approach recognizes, or accommodates, the observations that most people in the population will have nearly zero exposures and will be mobile during a lifetime. Since the resolution of the analytical methods used in the 1991 air monitoring contributes a significant oncogenic risk, a realistic oncogenic risk assessment must consider the true zero exposures. For example, the oncogenic risk from:

MLE and half LOD:	3.6E-07
UB and half LOD:	1.1E-06
MLE and half LOQ:	5.6E-07
UB and half LOQ:	1.7E-06

Lee *et al* (2002) [cited in HS 1805] did a more refined oncogenic risk for methidathion and other products and incorporated probabilistic methods, for which we commend them. Apart from our overarching disagreement with quantification of a cancer potency factor, as detailed above, we have several concerns with the calculated oncogenic risks.

Lee reports that methidathion-equivalents were calculated from the oxon and added to the parent methidathion. As discussed earlier, and recognized by DPR, the oxon concentrations exceeded parent concentrations and should not be considered. The Lee report therefore greatly overestimates methidathion exposures. Although Lee *et al* used distributions for many parameters in the exposure model, they did not present the model structure and we could not recreate the results - the work may be better evaluated if the full model is presented. Finally, while it may be scientifically correct to show oncogenic risks associated with different percentiles of exposure (Table 7), the public policy approach is to regulate based on the oncogenic risk associated with the per capita mean exposure. So, although we are encouraged by the Lee *et al* approach, we must conclude that the calculated risks are not reliable and overestimate risk for methidathion. (Note: the 50th percentile risk as calculated from overestimated air concentrations was 7E-07).

Based on the limited use of methidathion in California, and oncogenic risks approximating E-07 (Lee et al) in screening level assessments, there should be no doubt that realistic estimates of risk would be orders of magnitude lower. A refined assessment would show much lower risks, but we do not believe resources should be allocated to such an assessment. There should be no concerns about oncogenic risk and methidathion should not be a candidate toxic air contaminant.

Please contact me at the number below if further information is needed.

Respectfully,

Elizabeth Codrea

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cc: C. Baker